

REMARKS

I. Status of the Claims

Claims 1-54 were originally filed. Subsequently, claims 1-48 and 52-54 have been canceled, and claims 55-78 have been added.

Upon entry of the present amendment, claims 49, 55, 75, and 77 are amended to recite T1R2 or T1R3 having "a greater than 90% amino acid sequence identity" to a reference sequence. Support for this phrase can be found in the specification, *e.g.*, on page 11, line 29, to page 12, line 3. The word "modulates" in claims 49, 55, 75, and 77 is replaced with "activates or inhibits," support for which can be found in the specification, *e.g.*, on page 13, line 26, to page 14, line 15. The recitation of moderately or highly stringent hybridization conditions has been deleted from all claims. This amendment introduces no new matter.

Claims 49-51 and 55-78 are currently under examination.

II. Claim Rejections

A. 35 U.S.C. §112, Second Paragraph

Claims 31-33, 49-51, and 55-74 remain rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Specifically, the Examiner asserted that the terms "modulate" and "functional effect" are indefinite. Applicants respectfully traverse the rejection in light of the present amendment.

"Modulate"

Although Applicants do not agree with the Examiner's assertion that the meaning of the word "modulate" is ambiguous as to what it may encompass besides to activate or inhibit, in the interest of expediting prosecution, Applicants have amended the pending claims to replace "modulates" with the phrase "activates or inhibits." The indefiniteness rejection on this ground is thus obviated.

"Functional Effect"

The Examiner alleged that the term "functional effect" as recited in claims 55-78 is ambiguous. Applicants disagree.

35 U.S.C. §112, second paragraph, requires a claim to particularly point out and distinctly define the metes and bounds of the claimed subject matter. The determination of whether a claim satisfies this requirement is made from the standpoint of a person of ordinary skill in the pertinent art. As previously discussed in Applicants' response filed February 26, 2004, the specification provides a definition for "functional effect." On page 13, lines 1-7, for example, the specification states,

The phrase "functional effects" in the context of assays for testing compounds that modulate activity (e.g., signal transduction) of a sweet taste receptor or protein of the invention includes the determination of a parameter that is indirectly or directly under the influence of a GPCR or sweet taste receptor, e.g., a physical, phenotypic, or chemical effect, such as the ability to transduce a cellular signal in response to external stimuli such as ligand binding, or the ability to bind a ligand. It includes binding activity and signal transduction. "Functional effects" include *in vitro*, *in vivo*, and *ex vivo* activities.

On this same page as well as on pages 32 and 33, the specification further provides examples of such functional effects and describes various methods for determining the functional effects. These methods are all well known and routinely used by those skilled in the art and therefore allow artisans to readily determine such functional effects. While Applicants agree with the Examiner that these examples do not serve to limit the scope of the claims, Applicants contend that there is not ambiguity associated with the term "functional effect" when it is used in the context of screening for candidate compounds for their ability to activate or inhibit sweet taste signal transduction. The bounds of the claims are not merely subject to the interpretation of any individual, as the Examiner has contended; instead, a person of ordinary skill in the art of molecular and cellular biology would recognize the determination of changes in which parameters constitutes "functional effects" as such parameters are "indirectly or directly

under the influence of a GPCR or sweet taste receptor," as defined by the above-cited section of the instant specification.

Applicants submit that the term "functional effect," when used in combination with the description provided by the specification, adequately allows one of skill in the art to determine the metes and bounds of the claimed invention. The withdrawal of the indefiniteness rejection is respectfully requested.

B. 35 U.S.C. §112, First Paragraph

Claims 31-33, 49-51, and 55-74 remain rejected under 35 U.S.C. §112, first paragraph, for alleged lack of proper enablement. Applicants respectfully traverse the rejection in light of the present amendment.

According to the MPEP, to satisfy the enablement requirement, the information contained in a patent specification must be sufficient to inform one skilled in the relevant art how to both make and use the claimed invention. MPEP §2164. Whether the enablement requirement is met depends on whether undue experimentation is necessary for one of skill in the art to practice the invention in light of the disclosure. MPEP §2164.01.

The pending claims are drawn to methods for identifying activators or inhibitors of sweet taste signal transduction, using a sweet receptor as a reporter of altered signal transduction. As amended, the pending claims recite that the sweet receptor, a heterodimer of T1R3/T1R2, each of which having at least 90% sequence identity to a reference amino acid sequence, specifically binds a sweet compound, and that the functional effect of a candidate compound on the receptor indicates the compound's ability to activate or inhibit sweet taste signal transduction.

In the final Office Action mailed June 3, 2003, the Examiner asserted that while the specification enables the method for identifying activators or inhibitors of sweet taste signal transduction using a taste cell receptor composed of a heterodimer of SEQ ID NOs:9 and 15, when the receptor is present on the cell surface and is coupled to a Gα15 protein, the specification does not enable the claimed methods for identifying activators or inhibitors of

sweet taste signal transduction using a heterodimer sweet receptor comprising variants to SEQ ID NOs:9 and 15, or when the receptors are attached to a solid support, or for identifying "modulators." Applicants respectfully disagree with the Examiner.

a. T1R2 or T1R3 Variants

The amended claims define the T1R2 and T1R3 polypeptide sequences based on their percentage sequence identity (at least 90%) to reference sequences such as SEQ ID NO:15, 20, 23, or 25 and SEQ ID NO:7, 8, or 9. Applicants therefore submit that the T1R2 and T1R3 polypeptide sequences are clearly defined and allow the skilled artisans to readily prepare a polypeptide within the scope of a T1R2 or T1R3 variant. Given the state of art in the field of molecular biology, an artisan can easily produce such a T1R2 or T1R3 variant polypeptide. The teaching of functional features of the sweet receptor comprising T1R2 and T1R3 in the specification, *e.g.*, specific binding of the receptor to a sweet compound, allows a skilled artisan to easily test any heterodimer of T1R2 and T1R3 variants to verify whether such heterodimer would be suitable for use in the screening method of the present invention (*see, e.g.*, page 32 lines 17-35). These polypeptide variant production and functional screening processes require merely routine techniques and basic methods frequently used by those of skill in the art of molecular biology and protein chemistry that are often employed by a skilled artisan. Thus, Applicants contend that any experimentation necessary for generating T1R2 or T1R3 variants and determining which variants would be useful for practicing the claimed invention is routine and does not constitute undue experimentation.

In response to the Examiner's assertion that the specification is not enabling because it does not teach which positions of the exemplary T1R2 and T1R3 sequences may be modified to produce functional variants, Applicants submit that such explicit teaching of all potential amino acid modifications is not necessary for an artisan to practice the claimed invention. The taste receptor family GPCRs are well defined in structure and functional domains (*see, e.g.*, references C1-6 of IDS filed March 28, 2002), which allows a skilled artisan to choose appropriate locations for modifying the amino acid sequence. The present application particularly describes several inter-species orthologs of T1R2 and T1R3, *e.g.*, SEQ ID NO:15,

20, 23, or 25 and SEQ ID NO:7, 8, or 9. A person of skill in the art would be able to compare the amino acid sequences of these orthologs using a well known method, for example, computer-based sequence alignment, and identify certain regions or residues that are commonly conserved among the orthologs. An artisan would know that a variant operable for the present invention would likely be made by modifying one or more residues within a non-conserved region of an exemplary T1R2 or T1R3 sequence (*e.g.*, SEQ ID NO:9 or 15). Once a variant is made, whether it is suitable for use in the claimed method may be routinely verified based on its functional features as provided by the specification, *e.g.*, specific binding of the receptor to a sweet compound. Both variant production and functional verification utilize methods that are the type of experimentation routine done by artisans in the field.

Neither is the exhaustive teaching of all possible modifications of an exemplary T1R2 or T1R3 sequence practically possible. There exists a very large number of possibilities for modifying an exemplary sequence and ultimately achieving a variant polypeptide that is suitable for the purpose of practicing the claimed invention. The enablement requirement under 35 U.S.C. § 112, first paragraph, demands only sufficient teaching to allow an artisan to practice the claimed invention; there is never a requirement to name exhaustively all possible modifications.

b. Identifying Activators/Inhibitors when Receptor Is Not Present on Cell Membrane

The Examiner also stated that the claimed invention is not enabled because in the cases where the sweet receptor is not present in the cell membrane, the specification does not provide guidance as to what methods can be used to detect the receptor's response to a ligand. Specifically, the Examiner cited the paper by Lindemann (*Nature Medicine* 5:381-382, 1999) to support his doubt that functional characteristics of a G-protein coupled taste receptor can be studied in a cell-free system.

Applicants disagree with the Examiner for reasons previously presented (*see, e.g.*, page 14 of Applicants' response filed February 26, 2004). To address the Examiner's assertion that arguments of counsel alone cannot take place of evidence once the Examiner has advanced a

reasonable basis for questioning the disclosure, a declaration by inventor Dr. Charles S. Zuker pursuant to 37 C.F.R. §1.132 ("the declaration") is hereby submitted. In his declaration, Dr. Zuker attests that the cited reference describes some specific difficulties in assaying ligand specificity of a G-protein coupled receptor (GPCR) in a system where the GPCR is expressed in a heterologous host cell, such as GPCR degradation, cell surface expression, and correct protein conformation; yet the reference does not stand for the position that a cell-free assay system cannot be used to properly assess the functional features of a G-protein coupled taste receptor (Paragraph 6 of the declaration). Dr. Zuker further states:

There are various methods that can be used for detecting sweet taste signal transduction in a cell-free context, such as protein-protein binding assays, gel mobility shift assays, immunoassays, and enzymatic assays in a competitive or noncompetitive format. For example, the specification teaches measuring sweet taste signal transduction based on ligand-receptor binding, which is certainly suitable for practice in a cell-free assay system, such as the case where a sweet taste receptor is immobilized to a solid support.

(Paragraph 7 of the declaration)

It is therefore established that functional effects of a G-protein coupled taste receptor can be properly studied and measured in a cell-free system. An ordinarily skilled person in the art would be able to practice the claimed invention upon reading the present disclosure.

c. G-Proteins

The Examiner further alleged that the claimed invention is not fully enabled because the claims encompass the use of a sweet receptor coupled with an endogenous G-protein, yet the specification does not provide any G-proteins useful for the present invention besides Gα15, nor are such additional G-proteins known in the art.

Dr. Zuker attests in Paragraph 10 of his declaration that a number of G-proteins are known in the art as the promiscuous G-proteins that can couple a variety of GPCRs to downstream signaling effectors such as phospholipase C. For example, Offermanns and Simon (*J. Biol. Chem.*, **270**:15175-15180, 1995, Exhibit B of the declaration) describe promiscuous G-

proteins G α 15 and G α 16, which can be activated by a wide variety of GPCRs. Gustducin is another G-protein that is known to be involved in both bitter and sweet signal transduction (*see, e.g., Wong et al., Nature* **381**:796-800, 1996, Exhibit C of the declaration) and therefore can be used in the present invention. For the purpose of studying the functional effects of a GPCR, chimeric G-proteins based on a promiscuous G-protein (such as gustducin or G α 16) have also been made and used in cell-based assays (*e.g., Nelson et al., Cell*, **106**:381-390, 2001, reference C6 of IDS filed March 28, 2002).

Dr. Zuker further attests that in many cases, it is not even necessary to introduce an exogenous G-protein into an assay system to practice the claimed invention. For instance, endogenous G-proteins exist in taste cells and naturally couple with the T1R3-T1R2 taste receptor in signal transduction. Another example is a cell-free assay system, where the T1R3-T1R2 receptor alone, without any G-protein, can be used to screen for a potential taste modulator (Paragraph 11 of the declaration).

Applicants thus contend that the enablement rejection based on lack of description of G-proteins is improper and respectfully request that the rejection be withdrawn.

d. Modulator v. Activator or Inhibitor

Additionally, the Examiner took the position that the claimed invention is not enabled because the claimed methods are for identifying "modulators" of sweet taste signal transduction, whereas the specification teaches only the identification of activators or inhibitors.

As amended, the currently pending claims are now directed to a method for identifying compounds that activate or inhibit sweet signal transduction in taste cells. This particular issue raised by the Examiner is therefore moot.

In summary, no undue experimentation would be necessary to practice the invention as claimed. Accordingly, Applicants respectfully request that the enablement rejection under 35 U.S.C. §112 be withdrawn.

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Amdt. dated November 3, 2004
Reply to Office Action of June 3, 2004

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,


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